Apparatus for Determining the Rate of Drug Release from Solid Dosage Forms

D. C. BAUN and G. C. WALKER

Abstract □ Dissolution testing has assumed increasing importance over recent years. Current methods of evaluation are reviewed briefly and a new apparatus is presented for the determination of dissolution rate.

Keyphrases □ Dissolution, solid dosage forms—apparatus □ Apparatus, dissolution—new design □ Diagram—dissolution apparatus □ Tablet, capsule dissolution rates—apparatus comparison

Dissolution testing has assumed importance in product research and development in recent years. There has been controversy as to the usefulness and validity of the *in vitro* dissolution method as far as correlation with *in vivo* results is concerned but it is recognized that an *in vitro* test will give some indication as to the rate and extent of solution from solid dosage forms. Certainly the study of pharmaceutical formulation factors in the development of solid dosage forms is facilitated and once clinical evaluations and correlations have been made the test serves as a quality control procedure (2). The development of an *in vitro* method which can serve to predict the rate of absorption of a specific drug in tablet form would be the first step toward the development of similar *in vitro* methods for solid dosage forms of other drugs (1–4).

There have been a number of methods developed for the determination of *in vitro* dissolution rates. It is not the intention to review all the various apparatus and methods in detail but to report on the principal features of such devices. Dissolution apparatus commonly encountered in the pharmaceutical literature may be categorized generally as follows: (*a*) modifications of the USP tablet disintegration apparatus; (*b*) the oscillating tube apparatus; (*c*) the Levy-Hayes beaker apparatus; (*d*) the NF XII, 2nd supplement apparatus (rotating-bottle type); (*e*) the Büchner funnel apparatus; (*f*) the United States Food and Drug Administration apparatus (Wiley apparatus).

The USP tablet-disintegration apparatus (5) is based upon the apparatus designed by Gershberg and Stoll (6). Operating conditions for dissolution are generally similar to those in the USP (5) or BP (7) for tablet-disintegration tests and the major modification encountered is the replacement of the official 10-mesh screen by a 40- or 100-mesh screen to retain sizable tablet particles in the tube or basket-rack assembly. Huber *et al.* (8), Vliet (9), Cooper (10), Kaplan (11), Schroeter and Hamlin (12), Schroeter and Wagner (13), Lazarus *et al.* (14), Wensley *et al.* (15), and Kadar and Walker (16) used modifications of the USP tablet-disintegration apparatus for drug dissolution studies. Cook *et al.* (17) used a stationary "basket" dissolution apparatus with a separate stirrer for the medium based on information from the USP-NF Joint Panel on Physiological Availability.

The Levy-Hayes dissolution assembly (18) consists of a 400-ml. Pyrex Griffin beaker containing 250 ml. of dissolution fluid which is agitated by a three-blade polyethylene stirrer attached to an electronic-controlled stirring motor. Stirring rates of about 30 to 60 r.p.m. are used (19). This is sufficient agitation to obtain a homogeneous solution for sampling purposes yet low enough not to break down the "microenvironment" of the tablet being tested (20). Stirring apparatus using different stirrers, stirring rates, and containers for dissolution fluid and test preparations were used by Gibaldi and Feldman (21) and by Wood and Syarto (22). Pernarowski *et al.* (23) used a continuous-flow apparatus with a stirring mechanism and Castello *et al.* (24) have designed a stirring apparatus with multiple testing stations.

The tablet-disintegration apparatus of the British Pharmacopoeia 1948 and 1953 (25, 26) consisted of a sealed test tube 15.2 cm. (6 in.) in length and 2.54 cm. (1 in.) in internal diameter filled with water at 37°. The tablet to be tested is agitated by repeatedly inverting the tube in a water bath at 37° at such a speed that the tablet travels through the water without striking the ends of the tube. A similar method of agitating the tablet or capsule in dissolution fluid was used in the dissolution test procedure of Souder and Ellenbogen (27). The Erweka testing apparatus for disintegration (28) also involves a closed-tube system through which disintegration fluid is pumped at a given temperature. The 15.2-cm. diameter glass "gut" rotates on an axis in the perpendicular plane. The "gut" proper is about 40 cm. in cross section and holds approximately 300 ml. of test fluid.

The rotating-bottle apparatus and test procedure for prolonged-release preparations official in the National Formulary XII, 2nd Supplement (29) are based on the apparatus and method of Souder and Ellenbogen (27). Samples to be tested are sealed in cylindrical bottles with the dissolution medium. The bottles are rotated

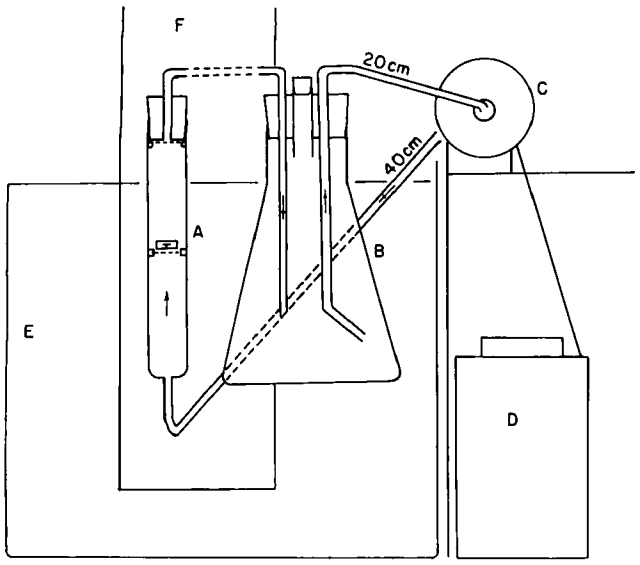

Figure 1—*Principal components of the constant circulation dissolution apparatus. See text for letter identification.*

end over end in a water bath at 37° and at a fixed rate. Variations of this procedure were used by Blythe (30), Campbell and Theivagt (31), Nessel *et al.* (32), Meyers (33), and Vora *et al.* (34). The bottle size varied and fluid volumes from 60 to 100 ml. were used. Rotation rates varied from 12 to 44 rotations per minute.

Nash and Marcus (35) proposed the Büchner funnel apparatus for screening experimental formulations of long-acting preparations and for control procedures. The test preparation was added to a fixed volume of dissolution fluid in a Büchner funnel fitted with a medium porosity fritted disk. The funnel was mounted on a suction flask and the test medium in the funnel agitated by a variable speed stirrer. Liquid samples to be assayed were drawn off periodically by suction into the flask.

Meyers (33) reported on a general procedure developed by Wiley of the United States Food and Drug Administration for evaluating sustained-action tablets. The apparatus consisted of a stoppered cylindrical tube with a glass wool filter above the bottom outlet and a side-arm outlet for return of fluid to a reservoir. A pump was used to circulate the fluid at a definite rate from the reservoir through the tube. The apparatus was immersed in a water bath at 37°. Tablets were placed on the filter and were separated from each other by layers of glass wool. Drug was eluted with 100-ml. aliquots of circulating dissolution fluid. Chaudhry and Saunders (36) used a replacement closed-tube method for evaluating sustained-action solid dosage forms. All apparatus discussed have a wide range of agitation intensity to which the test preparation is exposed. Filleborn (37) realized the need for low agitation intensities in predictive *in vitro* disintegration testing of solid oral dosage forms. Munzel and Kuhn (38) stated that the degree of agitation to be used in any *in vitro* procedure was one of the areas of greatest concern and difficulty. This was reiterated by Hamlin *et al.* (39). Levy (18, 20) observed that if tablets were exposed to greater agitation conditions than those to which the tablets were exposed in the stomach correlation of *in vitro* dissolution data with *in vivo* absorption data could not be made.

Marlowe and Shangraw (40) and Patel and Foss (41) used a tablet-dissolution apparatus consisting of a plastic cell having two compartments separated by a semipermeable membrane. Tablets were introduced into one compartment and dissolution fluid was placed in both compartments. The plastic cell was rotated at 15 r.p.m. in a water bath at 37°. A disadvantage of the apparatus noted by these investigators was the necessity of interrupting the rotation of the cell while samples were withdrawn.

Since no apparatus or procedure can exactly duplicate *in vivo* conditions, all dissolution studies are relative, and the most important considerations are those of reproducibility, practicality, and reasonableness (40). A suitable *in vitro* dissolution apparatus should be sufficiently versatile to handle a variety of solid dosage forms and should be a closed system. Lazarus *et al.* (14) have pointed out that the USP tablet disintegration apparatus, modified for dissolution rate determinations, showed a liquid loss of 20–25% over an 8-hr. period at 37°. A closed system is useful for testing low-density capsules and tablets which tend to float on the dissolution medium in open systems. It is of advantage if the dissolution procedure is not interrupted to remove and replace samples. Agitation at a fixed rate over long periods of time is necessary and the separation of the dissolved drug from the bulk of the product helpful. The volume of eluant should be large enough so that the drug concentration in the dissolution fluids does not exceed 10 to 20% of drug solubility. Dissolution rate-limited absorption of drug implies that there is no buildup of drug in the gastrointestinal fluids (42). Unless this "perfect sink" condition is embodied in the design of the *in vitro* test, the *in vivo* results will bear little relation to *in vivo* observations (21).

EXPERIMENTAL

Apparatus—An apparatus to provide a simple and reproducible method of determining rate of drug release from solid dosage forms was constructed. The principle was that of the Wiley apparatus as reported by Meyers (33) with several modifications. The principal components are shown in Fig. 1 and consist of a glass dissolution cell (A) in which is placed the tablet or product to be tested, a reservoir (B) for the dissolution medium, a continuous-duty oscillating pump (C),[1] controlled by a variable transformer (D),[2] sufficient lengths of glass and Tygon tubing (5.0 mm. i.d.) to connect the components, and a suitable water bath (E) in which the dissolution cell and reservoir are partially immersed. The bath consists of a cylindrical Pyrex jar [40.64 cm. (16 in.) o.d. and 30.48 cm. (12 in.) high or larger for reservoirs of greater capacity] filled with deionized water and regulated at 37 ± 0.1° by a thermostated circulating pump[3] (F). The reservoir and dissolution cell are held in place during the test run by two clamps attached to a retort stand. The pump is placed at the same elevation as the top of the reservoir. Rate of liquid flow through the cell is controlled by setting the variable transformer to a previously determined value.

Figure 2 delineates the dissolution cell and reservoir more clearly. The lower screen (a) of the dissolution cell is a 100-mesh stainless steel screen 1.8 cm. in diameter. The screen is held in place by two washers (Neoprene) having an opening 1.3 cm. in diameter and a rim

[1] Gorman-Rupp Industries Inc., Belleville, Ohio.
[2] Powerstat type 116.
[3] Haake, model ED.

thickness of 2 mm. The upper screen (b) of the cell is of the same size as the lower screen (a) but rests on one Neoprene washer and is easily removed. A stopper (Neoprene) (c), size 2, seals the dissolution cell and holds the upper screen in place. A short length of tubing (Tygon) (d) connects the elbow tubes of the dissolution cell and reservoir providing a flexible connection so that stopper (c) may be manipulated easily when the components of the apparatus are in their proper spatial arrangements prior to the start of the dissolution test. A stopper (Neoprene) (e) seals the glass tube (f) (5.0 × 0.8 cm. i.d.). Samples are withdrawn by pipet through this tube. A stopper (Neoprene) (g) seals the reservoir, a 250-ml. or 500-ml. wide-mouth conical flask. The stopper is fitted with the three glass tubes as shown. The dimensions of the elbow tubes in stopper (g) apply when the reservoir is a 500-ml. conical flask but will vary in length as the reservoir is made larger or smaller.

Procedure—The dissolution medium is poured into the reservoir and allowed to equilibrate with the water bath (37°). The pump is primed by allowing dissolution fluid to flow at a high rate through the pump into the lower part of the dissolution cell but not above the lower screen. This procedure expels air from the pump and tubing. The flow rate for the test liquid may be varied but a rate of 70 ± 2 ml./min. is satisfactory and is adjusted by means of the variable transformer. The tablet is dropped into the dissolution cell. The upper screen (b) is inserted and stopper (c) placed in position. The pump is started and the dissolution test begins. Samples are removed by pipet through tube (f) of the reservoir at specified time intervals for assay. An equal volume of dissolution fluid is added immediately by pipet through tube (f) to replace that withdrawn.

Preliminary dissolution determinations were performed on a variety of commercial tablets in an attempt to ascertain the usefulness of the method, particularly with reference to substances of low water solubility. A large number of tests were made but with casual assay data. Results are reported here of dissolution tests on compressed, uncoated tablets of two different brands of tolbutamide (500 mg.) and hydrochlorothiazide (50 mg.). A capsulated product containing granules of riboflavin was also evaluated. The Levy beaker method (18) was used for comparison purposes. All tests were made at a temperature of 37.5°.

Dissolution Tests—*Hydrochlorothiazide*—The assay for hydrochlorothiazide tablets was that of the BP 1963 (7). The apparatus described in this paper was fitted in the dissolution chamber with a

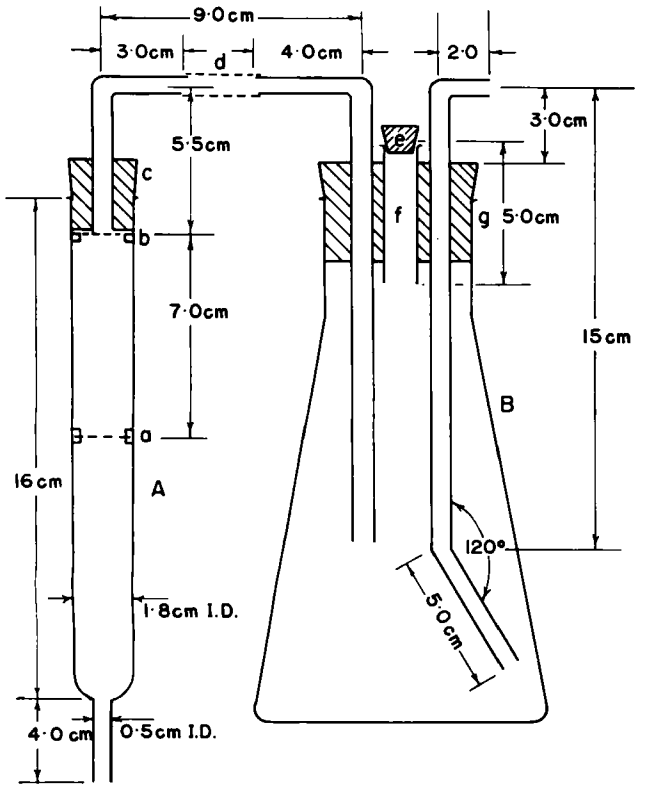

Figure 2—*Dissolution cell and reservoir of the constant circulation dissolution apparatus. See text for letter identification.*

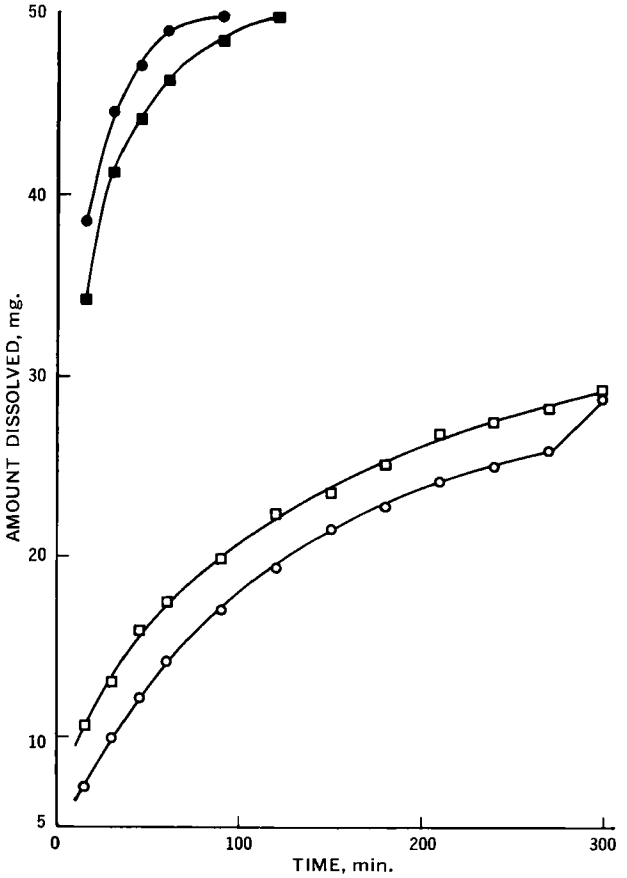

Figure 3—*Rate of dissolution of compressed tablets containing hydrochlorothiazide (50 mg.) with purified water as the dissolution medium. Key: ○, Levy method, Product A; ●, Levy method, Product B; □, constant circulation apparatus, Product A; ■, constant circulation apparatus, Product B.*

200-mesh screen on the top and a 100-mesh screen on the bottom. Screen mesh size may be varied to suit a particular dosage form or constituents of a given dosage form. The reservoir consisted of a 600-ml. conical flask. The rate of flow of dissolution fluid was 70 ml./min. which was found from the use of a large number of tablets to be the most suitable. Table I and Fig. 3 show the results of dissolution tests on two commercial brands of hydrochlorothiazide tablets using purified water as the dissolution medium and both methods of testing. The values in all studies reported were the average of six determinations (Products A and B) and corrected to

Table I—Results of Dissolution Tests on Compressed Tablets of Hydrochlorothiazide (50 mg.) with Purified Water as the Dissolution Medium[a]

Time, min.	Amount Dissolved, mg.[b] Levy Apparatus Product A	Levy Apparatus Product B	Constant Circulation Apparatus Product A	Constant Circulation Apparatus Product B
15	7.2	38.5	10.6	34.3
30	9.9	44.6	13.0	41.2
45	12.1	47.2	15.9	44.1
60	14.1	49.0	17.5	46.3
90	17.0	49.9	19.9	48.5
120	19.3		22.4	49.9
150	21.5		23.5	
180	22.8		25.1	
210	24.1		26.7	
240	25.0		27.6	
270	25.8		28.2	
300	28.8		29.1	
1500	37.2		38.8	

[a] Flow rate 70 ml./min. [b] Average of six determinations.

Table II—Results of Dissolution Tests on Compressed Tablets of Hydrochlorothiazide (50 mg.) with Simulated Intestinal Fluid as the Dissolution Medium (pH 7.5)[a]

Time, min.	Amount Dissolved, mg. Product A[b] Levy Apparatus	Constant Circulation Apparatus
30	6.4	4.9
60	10.1	8.5
90	13.0	10.8
120	15.1	11.9
150	16.9	14.1
180	18.4	15.5
210	20.0	16.9
240	21.1	18.0
270	22.3	19.2
300	23.5	20.1
660	31.2	27.2
1440		38.9
1560	39.0	

[a] Flow rate 70 ml./min. [b] Average of six determinations.

assay values made from analysis of three samples of 10 tablets each with a control prepared from an arbitrary mixture of excipients. Product A assayed 50.3 mg. and Product B 51.2 mg. Table II and Fig. 4 present the results of dissolution determinations on Product A but using simulated intestinal fluid at pH 7.5 (5) and both apparatus. Control determinations with intestinal fluid showed no assay interference. Product B showed complete dissolution after 10 min. and using both apparatus. A third compressed tablet, Product C, was also tested and the results were almost identical to those reported for Product B in both water and intestinal dissolution fluids. Table III shows the results obtained at pH 7.5 with Product A but using flow rates of 40 ml. and 100 ml./min. Dissolution may be influenced by the use of simulated gastric fluid. This was not pursued to any extent at this time but Product B using gastric fluid and a flow rate of 70 ml./min. showed complete dissolution in 8 min.

Tolbutamide—The assay for tolbutamide was that of the USP XVII (5) and the assay value with excipient control was secured as outlined under hydrochlorothiazide. The assay was 501.2 mg. for Product D. The dissolution method reported here used a 4,000-ml. conical flask as the reservoir. The dissolution chamber contained an upper screen of 200 mesh and a lower of 100 mesh. The flow rate was 70 ml./min. The Levy method used a 4,000-ml. beaker with the

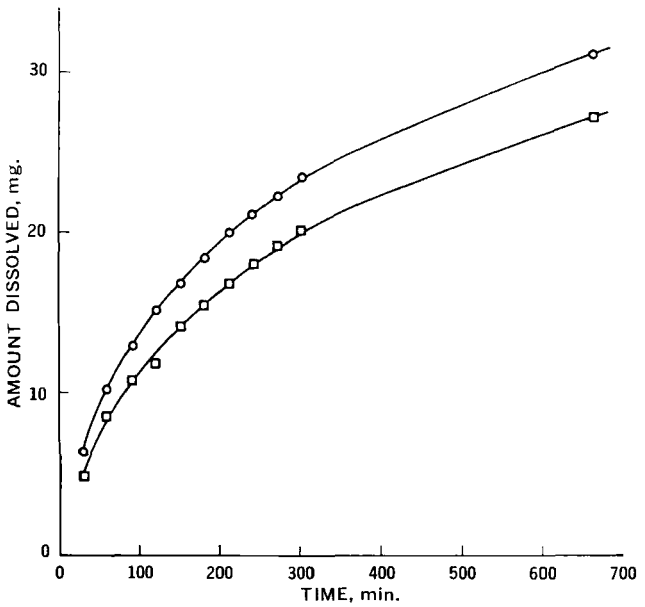

Figure 4—*Rate of dissolution of compressed tablets containing hydrochlorothiazide (50 mg.) with simulated intestinal fluid as the dissolution medium. Key: O, Levy method, Product A; □, constant circulation apparatus, Product A.*

Table III—Results of Dissolution Tests on Compressed Tablets of Hydrochlorothiazide (50 mg.) with Simulated Intestinal Fluid as the Dissolution Medium (pH 7.5) and Two Rates of Flow Other Than 70 ml./min. in the Constant Circulation Apparatus

Time, min.	Amount Dissolved, mg. Product A[a] 40 ml./min.	100 ml./min.
30	7.0	16.3
60	8.5	20.7
90	9.4	24.9
120	10.9	32.5
150	12.1	38.4
180	13.0	45.0
210	13.9	46.9
240	14.8	47.0
270	15.7	47.9
300	16.3	48.1
660	24.0	
1440	36.6	

[a] Average of three determinations.

stirrer placed 5 cm. above the tablet. The results are shown in Table IV with Product D using purified water as the dissolution medium and the constant circulation apparatus only. Tests of Product D under similar conditions but in simulated intestinal fluid were very rapid. Tests were made on another brand of tolbutamide (Product E) using water and both methods of test (Table V, Fig. 5). The product assayed 502.3 mg.

Riboflavin—Results are presented here, in part, on granules of riboflavin since this is the subject of another publication concerned with sustained release and the use of this equipment. Hard gelatin capsules (No. 4) containing granules of riboflavin were prepared from a precompressed mass (16/20 mesh) using the following formula: riboflavin 10 mg., magnesium stearate 6.2 mg., and water-soluble resin[4] 8 mg. The mixture (80 mesh) was precompressed at 10,000 kg. in a Carver press and broken up to give particles which passed through a No. 16 sieve but not a No. 20. The encapsulated granules were tested using both methods and water (Table VI).

RESULTS AND DISCUSSION

A flow rate of 70 ± 2 ml. of liquid through the dissolution cell of the apparatus was accepted arbitrarily since this rate of flow produced a gentle, undulatory motion of a tablet. A tablet rests on the lower screen and any tablet fragments stay in close proximity to the bulk of the tablet. Tablets are subjected to agitation of a similar intensity to that used in the Levy-Hayes beaker method but to a much lower agitation intensity than that occurring in the oscillating tube and modified USP tablet-disintegration test methods. Levy

Table IV—Results of Dissolution Tests on Compressed Tablets of Tolbutamide (500 mg.) with Purified Water as the Dissolution Medium and Using the Constant Circulation Apparatus[a]

Time, min.	Amount Dissolved (to the nearest mg.) Product D[b]
8	102
38	325
68	449
98	499

[a] Flow rate 70 ml./min. [b] Average of three determinations.

(19, 20) and Edwards (42) have presented evidence showing that solid dosage forms are exposed to relatively low agitation intensities following oral administration. Filleborn (37) was aware of the gentle agitation conditions in the human stomach and constructed an "artificial stomach" in which *in vitro* disintegration times showed correlation with *in vivo* disintegration times. Munzel and Kuhn (38) state that the degree of agitation influences dissolution rates in fast-release preparations, but may have a minimal effect in sustained-

[4] Carbopol, Goodrich Rubber Co., Cleveland, Ohio.

Table V—Results of Dissolution Tests on Compressed Tablets of Tolbutamide (500 mg.) with Purified Water as the Dissolution Medium and Using Both Dissolution Test Apparatus[a]

Time, min.	Amount Dissolved, mg. Product E[b] Levy Apparatus	Constant Circulation Apparatus
30	45.0	100.0
60	79.9	164.8
90	110.2	209.9
120	128.8	244.6
150	139.7	264.8
180	150.0	276.3
210	158.6	291.3
240	162.1	298.7
270	164.4	310.0
300	166.0	325.3
400		377.0

[a] Flow rate 70 ml./min. [b] Average of six determinations.

release preparations since diffusion from within a particle or matrix may be the controlling step in rate of drug release. Hamlin *et al.* (39) indicated that only low agitation rates could adequately differentiate rate of release from solid dosage forms when correlated with the *in vivo* data available to them.

The constant circulation apparatus may be useful in dissolution determinations. It is possible to vary screen size in the dissolution chamber, and the size of the chamber itself, if such is deemed necessary, for different size dosage forms. Glass filters may be used and standard taper glassware may facilitate assembly and provide elegance. Any suitable pump may be used with nonreactive working parts and which provides an even flow. The flow rate may be varied and as would be expected, there is a variation in rate of solution with such change. Specifications as to size of constituent parts has been made and these could vary of course but should be standardized in light of reproducibility and laminar and turbulent flow. Stock glassware and accessories would be an advantage and the cost should be reasonable.

The use of any size reservoir makes it possible to achieve solutions of any degree of saturation. Such conditions may be useful in the design and evaluation of pharmaceutical formulations, particularly in the correlation with *in vivo* results and the "perfect sink" conditions presented in the literature. Mixing may be provided by a suitable stirring mechanism in the reservoir or perhaps a magnetic stirring device. Excipient matter to date has provided no impediment. The tablet performance is visible at all times. For the most part, tablets remain on the bottom screen but depending on density, trapped air, *etc.*, may rise and rub against the upper screen, thus influencing dissolution. The test fluid may be introduced through the top screen but no data are presented at this time with reverse flow other than to say that it would be useful with certain lower density types of dosage forms. The introduction of an opposing stream of dissolution fluid from the top of the chamber, with suitable chamber design, might provide a suspended system, but this has not been investigated.

Table VI—Results of Dissolution Tests on Granules of Riboflavin Contained in No. 4 Hard Gelatin Capsules and Using Purified Water as the Dissolution Medium[a]

Time, min.	Amount Dissolved, mg.[b] Levy Apparatus	Constant Circulation Apparatus
20	2.1	2.0
65	4.1	3.8
90	5.7	4.3
150	7.4	5.6
225	7.6	6.5
300	8.9	7.1
360	9.3	7.4
390	9.6	7.8
1320	9.8	8.0

[a] Flow rate 70 ml./min. [b] Average of three determinations.

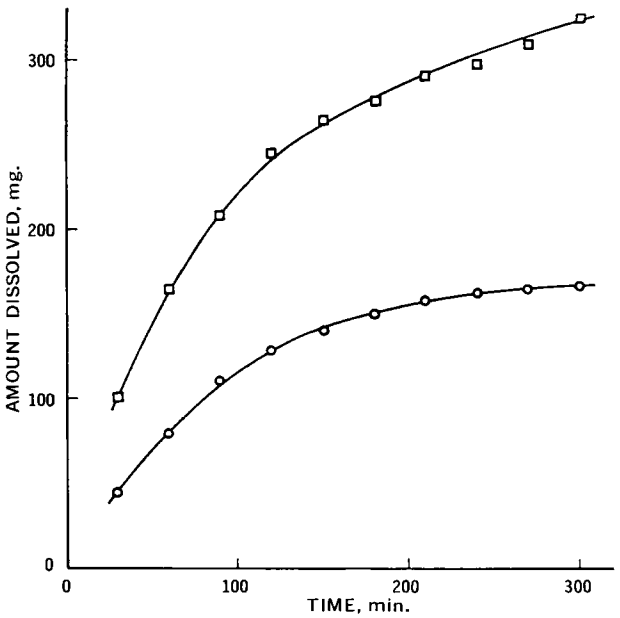

Figure 5—*Rate of dissolution of compressed tablets containing tolbutamide (500 mg.) with purified water as the dissolution medium. Key: O, Levy method, Product E; □, constant circulation apparatus, Product E.*

The apparatus is closed and sample removal is simple. A pH gradient-dissolution may be used by introducing fluids of varying pH at a constant rate or constant volume and such procedure is important in dissolution determinations. While not perhaps relevant to the apparatus discussion, it has been felt in these laboratories that dissolution fluid should involve some simple substance such as a cellulose or a gum in order to impart a mucous-like effect and varying viscosity to the dissolution media which may then simulate conditions in the gastrointestinal tract more closely. It is not unreasonable to project a return to bile salt in light of the comments made as to surfactant effect. The apparatus lends itself to automation and the passage of effluent through suitable recording devices for continuous measurement. Preliminary trials would suggest satisfactory results with sustained-release dosage forms and with coated dosage forms.

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Tableting Properties of a Directly Compressible Starch

KRISHNA S. MANUDHANE*, AVINASH M. CONTRACTOR, HYO Y. KIM, and RALPH F. SHANGRAW

Abstract □ Tableting properties of a directly compressible starch are investigated. This starch appears to have many advantages over starch USP with respect to fluidity and compressibility and as such would be useful in direct compression. In addition, compressible starch gives results comparable to USP starch in terms of disintegration time and dissolution rate when used at equivalent levels. The high moisture content of compressible starch does not affect the stability of aspirin when compressed together. Amylose is shown to be the effective component of starch in terms of its disintegrant effect. Doubt is cast on the role of starch grain swelling in tablet disintegration.

Keyphrases □ Starch, directly compressible—tableting properties □ Flow properties—compressible starch □ Dosage forms, compressible starch—high, low drug content □ Stability—directly compressible starch dosage forms □ Dissolution, disintegration—compressible starch tablets

Of the various methods available for the production of tablets, direct compression offers a number of advantages, particularly in regard to ease and economy of manufacture and increased product stability. Since the majority of drugs lack either sufficient bulk, satisfactory compression characteristics, or flow properties, it is necessary to utilize suitable excipients to impart such properties to the tablet formulation. However, the number of filler-binders reported to be useful for direct compression is quite limited. These include spray-dried lactose, anhydrous lactose, microcrystalline cellulose, and amylose (1–5). The need to evaluate new filler-binders is, therefore, obvious. A variety of starch[1] has recently been suggested for use as a filler-binder in direct compression. This starch is claimed to be relatively fluid, and does not require a lubricating agent when compressed alone. The possibility that the directly compressible starch might be a useful filler-binder in direct compression warranted an evaluation of its tableting properties.

A list of typical properties of the compressible starch (6) are summarized in Table I. Chemically, compressible starch does not differ from starch USP.

EXPERIMENTAL

Effect of Environment on Hardness and Disintegration Time—A study of variations in hardness and disintegration time caused by environment was conducted on tablets compressed to a constant thickness by means of a rotary press (Colton model 216) using 1.58 cm. ($^5/_8$-in.) dies and flat-faced punches. The tablets were divided into two groups and stored at a high temperature (60°), and high relative humidity (60% at 40°) for a week and changes in hardness and disintegration time noted. The results are presented in Table II.

Flow Properties—To study the effects of glidants on the fluidity of the compressible starch, two commonly used flow conditioners (pyrogenic silica[2] and hydrated sodium silico-aluminate[3]) were tried. Two-kilogram batches of the glidant and the compressible starch were blended (Patterson-Kelly Twin Shell Blender,

[1] Marketed as Sta-Rx 1500 Starch by A. E. Staley Mfg. Co., Decatur, Ill.

[2] Colloidal silicon dioxide, marketed as Cab-O-Sil by Cabot Corp., Boston, Mass.

[3] Marketed as Zeolex by J. M. Huber Corp., New York, N. Y.